IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Earl et al**

Application No: **10/612,014** Group Art Unit: **1625**

Filed: **July 3, 2003** Examiner: **E. Huang**

For: **Nitrosated Nonsteroidal Antiinflammatory Compounds, Compositions and Methods of Uses**

Attorney Docket No: **102258.156 US1**

Commissioner of Patents
PO Box 1450
Alexandria, VA 22313-1450

Petition from Requirement for Restriction under 37 C.F.R. § 1.144

Applicants petition under 37 C.F.R. § 1.144 from the Examiner's final restriction requirement set forth in the Office Action dated December 30, 2004.

I. The Restriction Requirement

On May 27, 2004, the Examiner made a four-way restriction requirement of pending claims 1-58. Applicants traversed the Examiner's four-way restriction requirement on June 17, 2004, and provisionally elected Group I with traverse.

On September 3, 2004, the Examiner issued another fifty seven-way restriction requirement. On October 27, 2004, Applicants traversed the Examiner's restriction requirement and proposed a new two-way restriction requirement directed to the compounds of Formula (I) or Formula (II). Applicants provisionally elected Examiner's Group X with traverse.

In the office action dated December 30, 2004, the examiner maintained the fifty seven-way restriction requirement and issued a further restriction requirement. The Examiner clarified the Restriction Requirement and then made the fifty six-way restriction requirement final.

This Petition is timely filed: Applicants requested reconsideration under 37 C.F.R. § 1.143 and made a provisional election with traverse.

II All the Pending Claims are Related

All the pending claims are related. In particular, pending claims 1-58 all require a compound that is a **nitrosated nonsteroidal antiinflammatory compound of Formula I**

Applicants pending claims with respect to the restriction requirement for the compounds of Formula (I) are outlined below. The pending claims, as amended to comply with the further restriction for variable "X" in the compounds of Formula (I), are attached hereto as Appendix 1.

The Examiner's restricted the invention as follows:

Group I	Claims 1-4, 55, 56 in part	Compound of Formula I wherein R_n is a theinyl of Formula 1 or 10
Group II	Claims 1-4, 55, 56 in part	Compound of Formula I wherein R_n is a keto group Formula 2, 17, 22, 27 or 38
Group III	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is an isoindoyl of Formula 3
Group IV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a heterocyclic tricyclic group of Formula 4 or 51
Group V	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a pyrrolyl of Formula 5
Group VI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a S(O)s containing group of Formula 6
Group VII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a halo containing group Formula 7
Group VIII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a indolyl Formula 8, 23 or 24
Group IX	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a carboxzolyl of Formula 9 or 28
Group X	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is an ether containing group of Formula 11, 12 or 19
Group XI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is an imidazopyridine of Formula 13
Group XII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a 1,3 oxazolyl of Formula 14, 39 or 49
Group XIII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a hydrocarbyl of Formula 15 or 35
Group XIV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is an amine containing group of Formula 16, 20 or 25

Group XV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a carboxylic ester containing group of Formula 18
Group XVI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a benzoxazolyl of Formula 21 or 42
Group XVII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a benzopyrazolyl of Formula 26
Group XVIII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a pyrrolyl of Formula 29, 33 or 45
Group XIX	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a pyrazolyl of Formula 30, 31, 40 or 47
Group XXI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a pyrrolyl of Formula 32 or 43
Group XXII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a benzopyranylpyridinyl of Formula 34
Group XXIII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is an oxygen containing tricyclic ring of Formula 36 or 37
Group XXIV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a 1,2 thiazolyl of Formula 41 or 46
Group XXV	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is a sulfur containing tricyclic ring of Formula 44
Group XXVI	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is an amido containing group of Formula 48
Group XXVII	Claims 1-4, 55, 56 (in part)	Compound of Formula I wherein R_n is an NOH containing moiety of Formula 50
Group XXVIII	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R_n is an amino containing group of Formula 1, 2, 9, 12, 15, 18 or 19
Group XXIX	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R_n is a hydroxy containing group of Formula 3, 4, or 11
Group XXX	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R_n is a carboxy ester containing group of Formula 5, 6, or 17
Group XXXI	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R_n is a nitrogen containing bicyclic group of Formula 7

Group XXXII	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R_n is a benzoindolyl of Formula 8
Group XXXIII	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R_n is a pyridinyl of Formula 10 or 16
Group XXXIV	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R_n is a indolyl of Formula 13
Group XXXV	Claims 1-4, 55, 56 (in part)	Compound of Formula II wherein R_n is a chloro containing group of Formula 14
Group XXXVI	Claim 5	Method of treating or reducing inflammation, pain or fever using the compounds of Formula I or II
Group XXXVII	Claims 6, 7	Method for treating a gastrointestinal disorder using the compounds of Formula I or II
Group XXXVIII	Claims 8, 9	Method of treating for facilitating wound healing using the compounds of Formula I or II
Group XXXIX	Claim 10	Method of treating or reversing gastrointestinal, renal and/or respiratory using the compounds of Formula I or II
Group XL	Claims 11-14	Method of treating for an inflammatory disease using the compounds of Formula I or II
Group XLI	Claim 15	Method of treating for an ophthalmic disorder using the compounds of Formula I or II
Group XLII	Claims 16, 17	Compositions comprising the compounds of Formula I or II of claim 1 and at least one additional therapeutic agent
Group XLIII	Claim 18	Method of treating or reducing inflammation, pain or fever using the composition of claim 16
Group XLIV	Claims 19, 20	Method for treating a gastrointestinal disorder using the composition of claim 16
Group XLV	Claims 21, 22	Method for facilitating wound healing using the composition of claim 16
Group XLVI	Claim 23	Method of treating or reversing gastrointestinal, renal and/or respiratory toxicity using the composition of claim 16
Group XLVII	Claims 24-27	Method for treating an inflammatory disease using the composition of claim 16

Group XLVIII	Claim 28	Method for treating an ophthalmic disorder using the composition of claim 16
Group XLIX	Claims 29-37	Compositions comprising the compounds of Formula I or II of claim 1 and at least one nitric oxide donor compound
Group L	Claims 38, 39, 58	Compositions comprising the compounds of claim 29 and at least one therapeutic agent
Group LI	Claim 40	Method of treating or reducing inflammation, pain or fever using the compositions of claim 29 or 38
Group LII	Claims 41, 42	Method for treating a gastrointestinal disorder using the composition of claim 29 or 38
Group LIII	Claims 43, 44	Method for facilitating wound healing using the composition of claim 29 or 38
Group LIV	Claim 45	Method of treating or reversing gastrointestinal, renal and/or respiratory toxicity using the composition of claim 29 or 38
Group LV	Claims 46-49	Method for treating an inflammatory disease using the composition of claim 29 or 38
Group LVI	Claim 50	Method for treating an ophthalmic disorder using the composition of claim 29 or 38
Group LVII	Claims 51-54, 58	Kits comprising the compound of claim 1 or 55, or a composition thereof with additional active ingredients

III. Restriction is Not Proper When the Claims are Related

As stated in MPEP §808.02, "[w]here, as disclosed in the application, the several inventions claimed are related, and such related inventions are not patentably distinct as claimed, restriction under 35 U. S. C. §121 is never proper (MPEP §806.05)."

All the pending claims are related. Thus, the restriction requirement is not proper. To show that the inventions are distinct, the Examiner must show either that (1) there is a separate classification of the claims; (2) a separate status in the art when they are classifiable together; or (3) a different field of search. *In re Kase*, USPQ2d 1063 (US PTO Director, 2004).

None of these three criteria have been shown with the claims of this application:

If the nitrosated nonsteroidal antiinflammatory compounds are allowable, then all the compositions requiring a nitrosated nonsteroidal antiinflammatory compounds would also be allowable and all the methods of use for these compositions would also be allowable. In other words, every pending claim that requires a **nitrosated nonsteroidal antiinflammatory compound** would also be allowable**.** *In re Kase*, USPQ2d 1063 (US PTO Director, 2004).

A search of the prior art for the nitrosated nonsteroidal antiinflammatory compounds would necessarily encompass a search of the prior art for the compositions for the nitrosated nonsteroidal antiinflammatory compounds, and, optionally, other compounds, and their methods of use. Thus, the prior art for the nitrosated nonsteroidal antiinflammatory compounds of Groups I–XXVII of Formula I or Groups XXVII to XXXV of Formula II respectively, will also be the same prior art for the compositions, methods of use and kits for the nitrosated nonsteroidal antiinflammatory compounds (i.e., Groups XLIX – L or Groups XXXVI to XLVIII and Groups LI to LVII or Group LXVI).

The claims in the pending application are generally directed to nitrosated nonsteroidal antiinflammatory compounds of Formula I or Formula II, and compositions comprising nitrosated nonsteroidal antiinflammatory compounds, and, optionally, other compounds, and the methods of use for the compounds and/or compositions.

Additionally, applicants respectfully submit that the Patent Office has failed to properly follow the MPEP guidelines for unity of invention within a Markush group. MPEP §803.02 states (Emphasis added):

> "Broadly unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility"

The Examiner failed to appreciate that the compounds of Formulas (I) or (II) are recognized classes of chemical compounds (i.e., nonsteroidal anti-inflammatory compounds) and there is an expectation from the knowledge in the art that members of this class (i.e., nonsteroidal antiinflammatory compounds) will behave in the same way in the context of the claimed invention.

IV. Examination of Additional Species

Pursuant to MPEP §803.02, Applicants respectfully request the examination of additional species upon an indication of the allowability of the elected species in claim 1. MPEP §803.02 states that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended [to the non-elected species]....The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim".

The Examiner in the Office Action dated December 30, 2004, stated that publications WO 02/092072 A2 and WO 03/013499 A2 are devoid of the "X" linker choice of the elected invention, i.e., Rn is variable 11, 12 or 19 in the compounds of Formula (I) in claim 1. These PCT applications disclose nitrosated non-steroidal anti-inflammatory compounds. Hence the Examiner has already searched other nitrosated non-steroidal anti-inflammatory compound directed to the non-elected species of the present invention. Expanding the claims to encompass these and other non-elected species would not be a burden to the Examiner.

Applicants respectfully request rejoinder of the non-elected species of claim 1, wherein Rn is variable 1-10, 13-18 and 20-51.

V. Rejoinder of Claims

Applicants respectfully request rejoinder of claims 5-54 and 56-58.

The claims in the pending application are generally directed to nitrosated nonsteroidal antiinflammatory compounds, and compositions comprising nitrosated nonsteroidal antiinflammatory compounds, and, optionally, other compounds, kits and the methods of use for the compounds and/or compositions.

If the nitrosated nonsteroidal antiinflammatory compounds of claims 1-4 are allowable, then all the compositions and kits requiring a nitrosated nonsteroidal antiinflammatory compounds would also be allowable and all the methods of use for these compositions would also be allowable. In other words every pending claim that requires a **nitrosated nonsteroidal antiinflammatory compound of claims 1-4** would also be allowable.

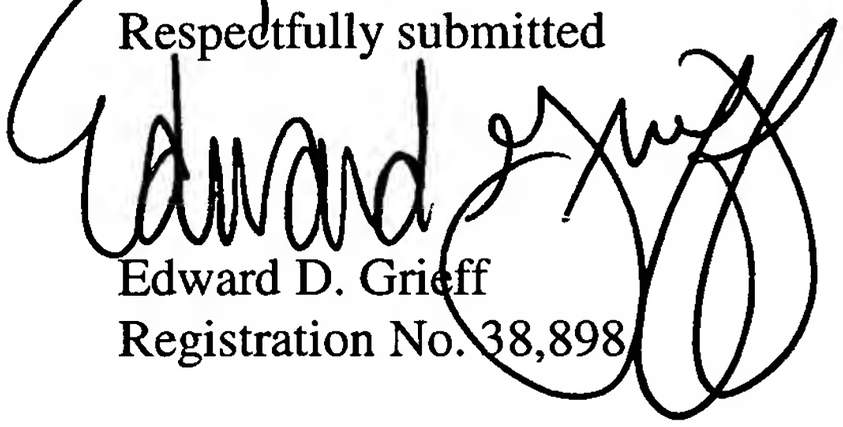
Additionally, a search of the prior art for the nitrosated nonsteroidal antiinflammatory compounds of claims 1-4 would necessarily encompass a search of the prior art for the compositions for the nitrosated nonsteroidal antiinflammatory compounds, and, optionally, other

compounds of claims 29-39, kits of claims 51-54 and their methods of use of claims 5-28 and 40-50. Thus, the prior art for the nitrosated nonsteroidal antiinflammatory compounds of claims 1-4, will also be the same prior art for the compositions, kits and methods of use for the nitrosated nonsteroidal antiinflammatory compounds of claims 1-4

VI. Conclusion

Applicants respectfully request that the restriction requirement be with drawn, that the examination of claim 1 is expanded to include the non-elected species and that pending claims 1-58 be examiner together in the present application.

Respectfully submitted



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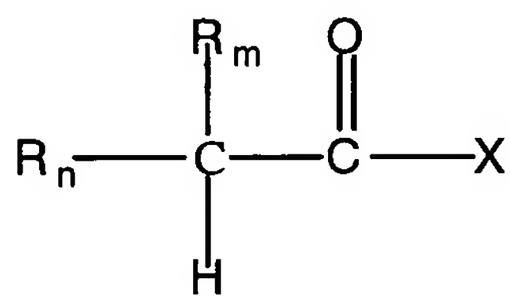
Appendix 1 – Pending Claims as of March 2005

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof; wherein the compound of Formula (I) is:



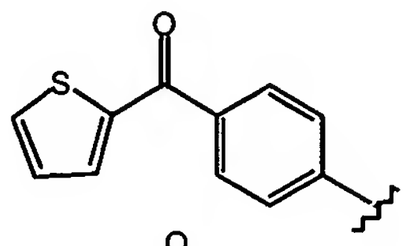
(I)

wherein:

R_m is a hydrogen or a lower alkyl group;

R_n is:

(1)



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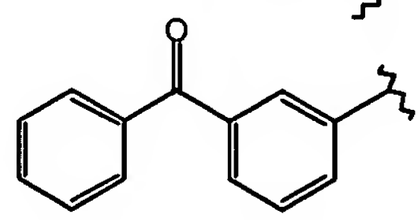

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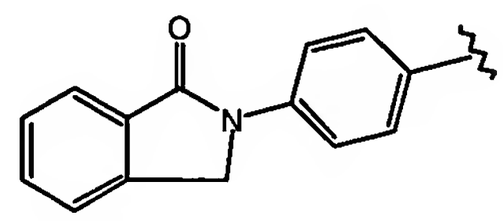

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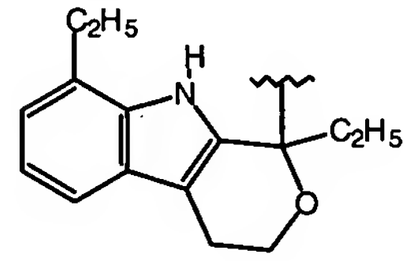

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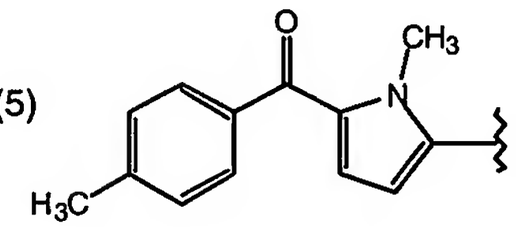

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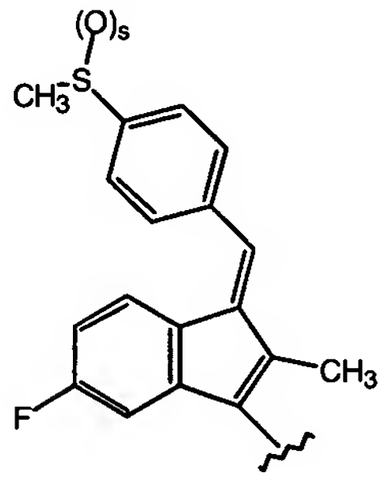

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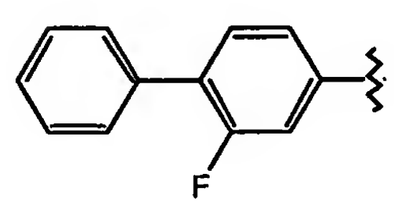

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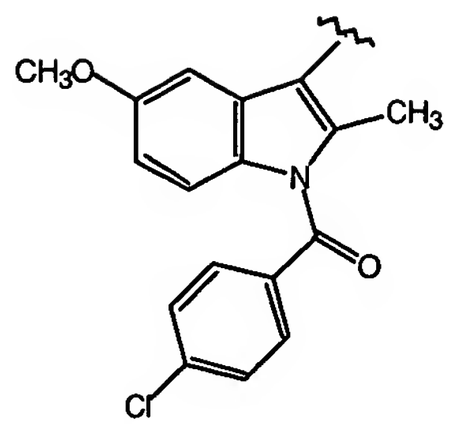

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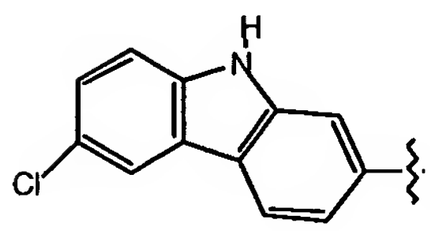

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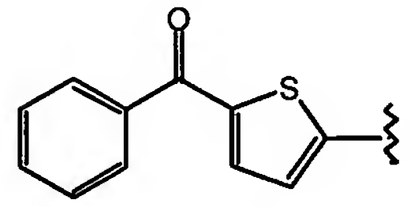

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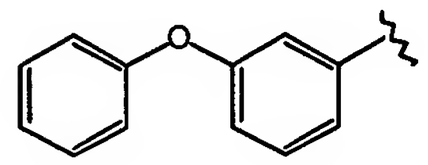

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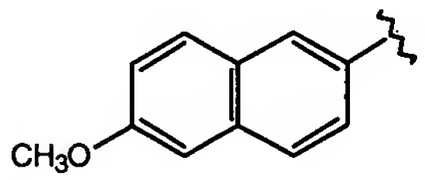

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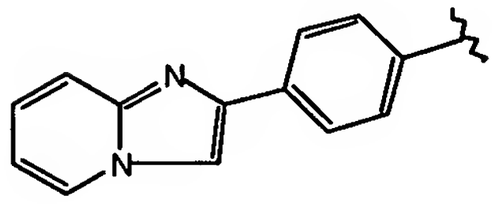

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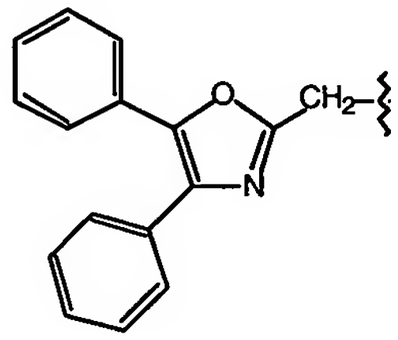

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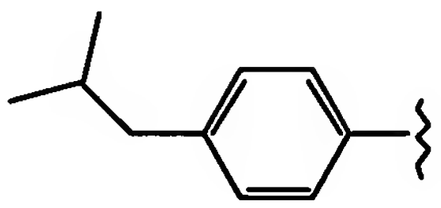

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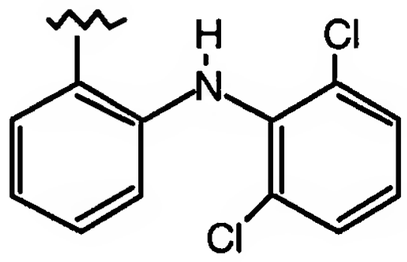

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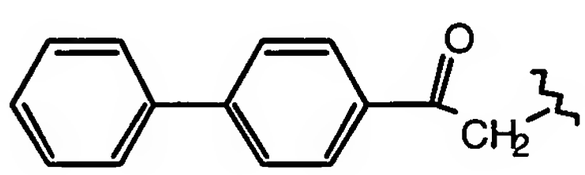

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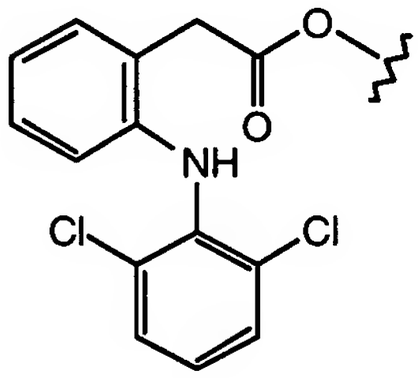

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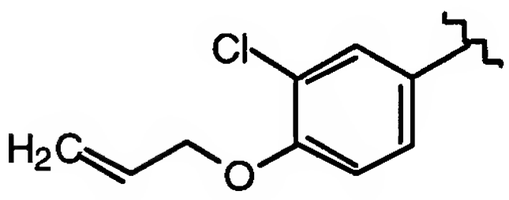

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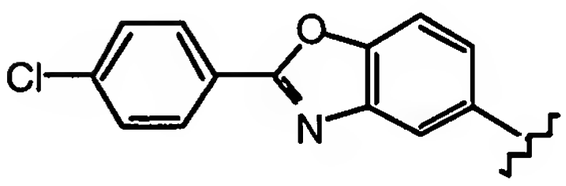

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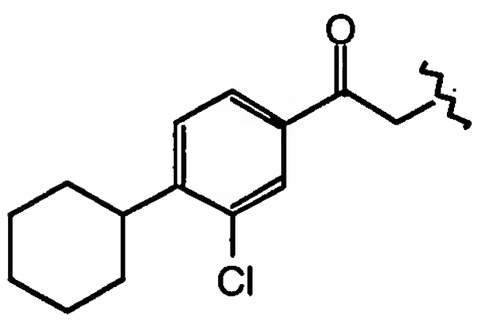

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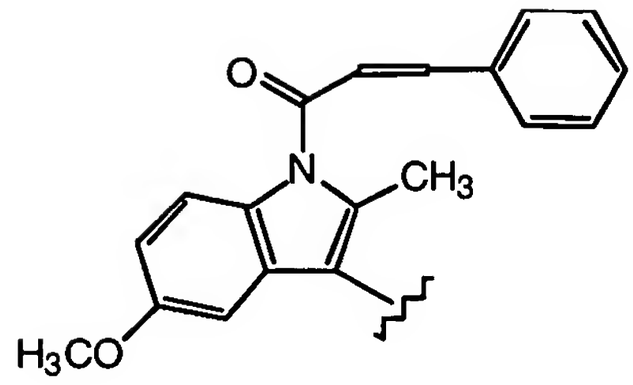

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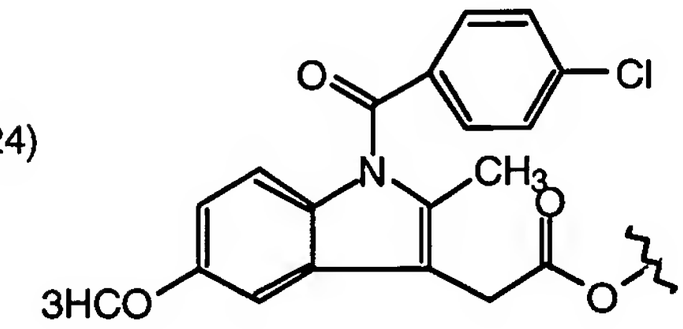

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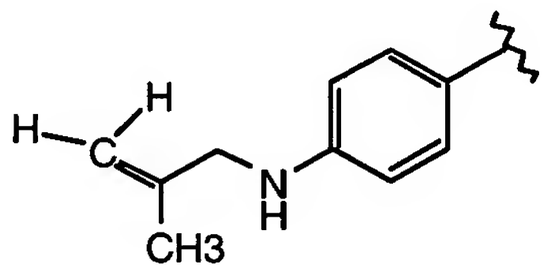

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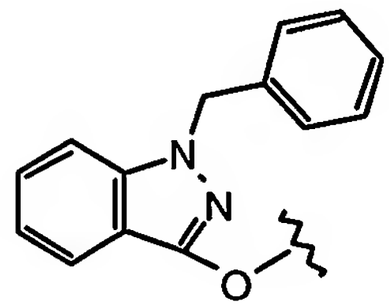

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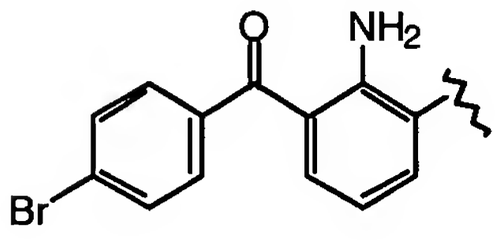

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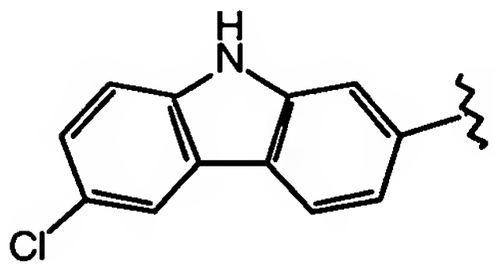

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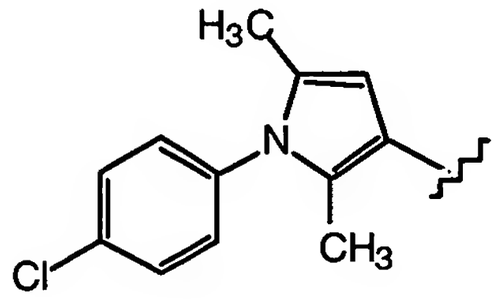
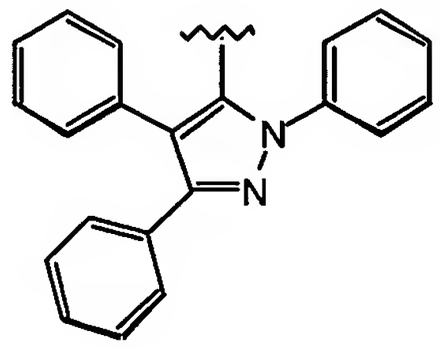
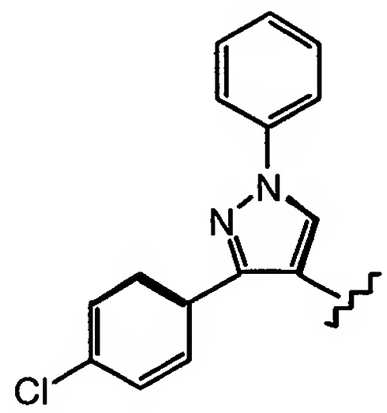
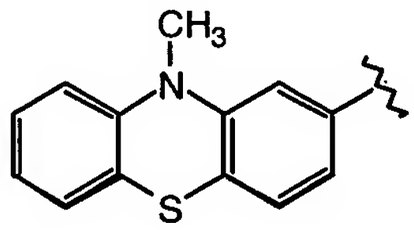
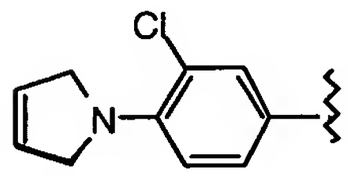
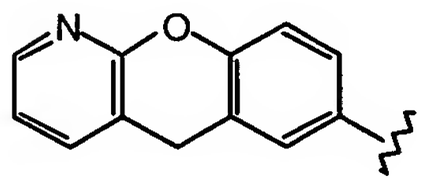


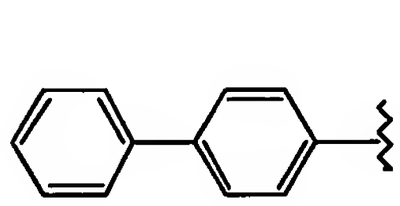
(30) 

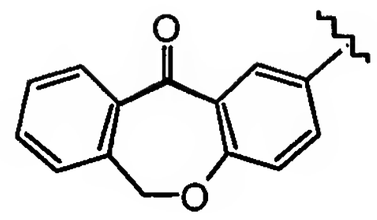
(31) 

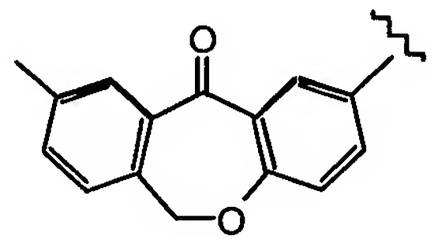
(32) 

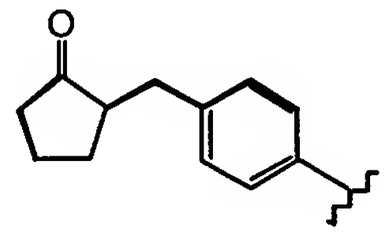
(33) 

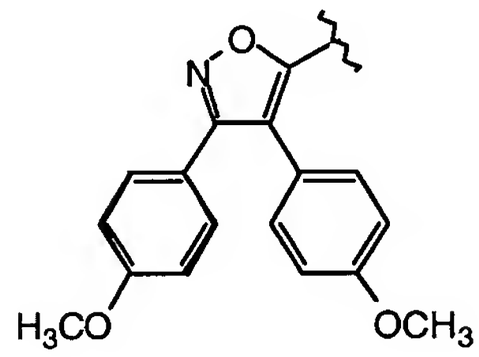
(34) 

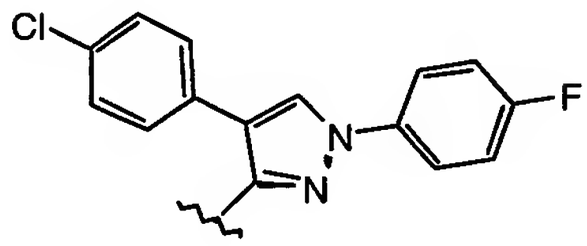
(35) 

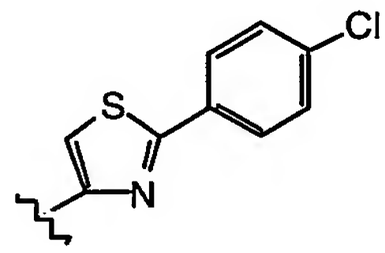
(36) 

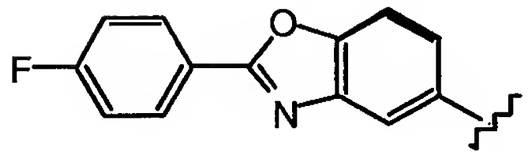
(37) 

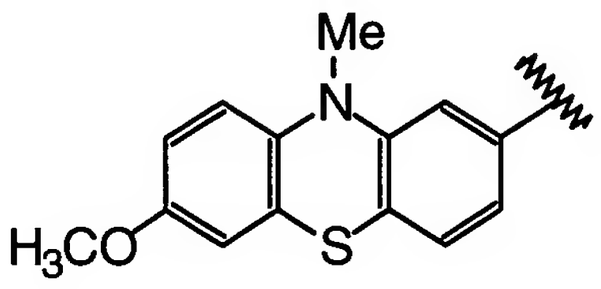
(38) 

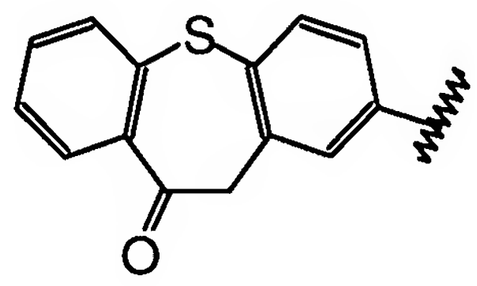
(39) 

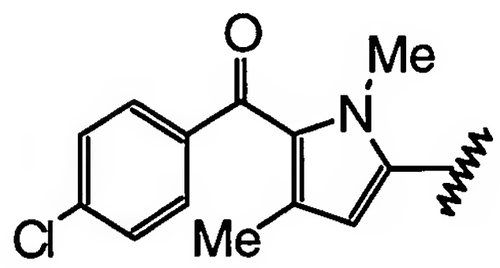
(40) 

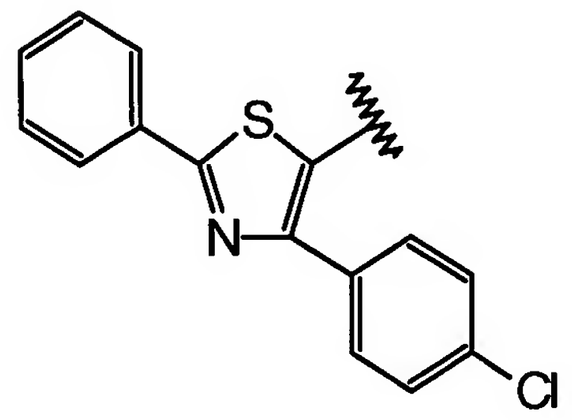
(41) 

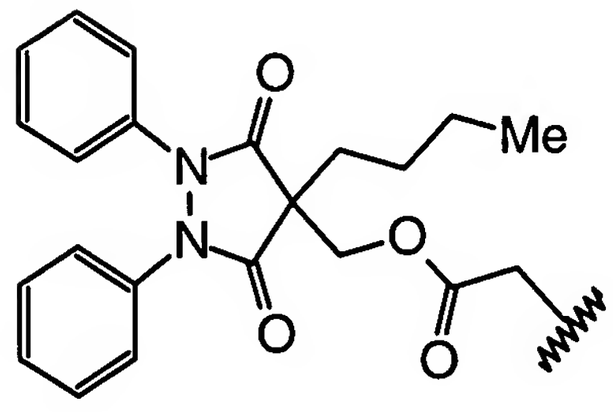
(42) 

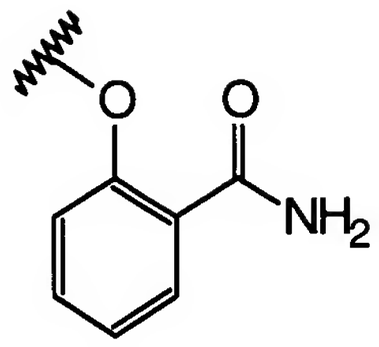
(43) 

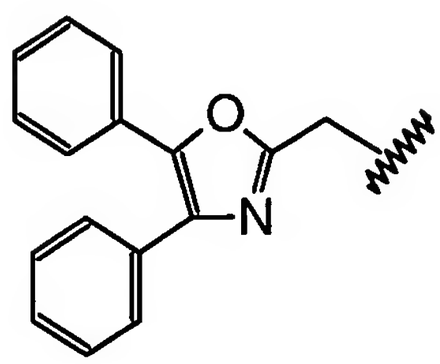
(44) 

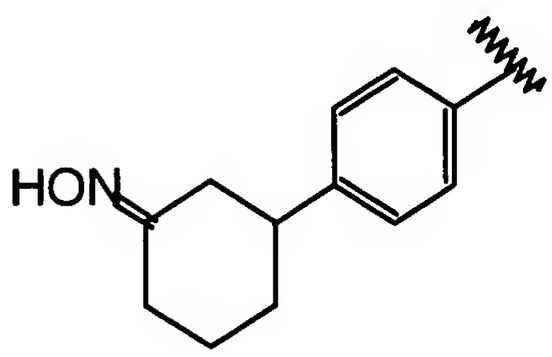
(45) 

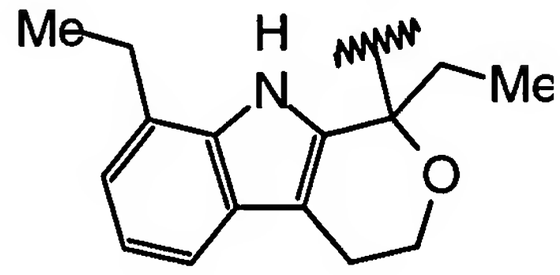
(46) 

(47) 

(48) 

(49) 

(50) 

(51) 

s is an integer of 0 or 1;

X is:

(1) $-Y-(CR_4C_4')_p-V-B-T-(CR_4R_4')_p-ONO_2$;

(2) $-Y-(CR_4R_4')_p-T-C(O)-(CR_4R_4')_o-(CH_2)-ONO_2$;

(3) $-Y-(CR_4R_4')_p-T-(CH_2)_q-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(4) $-Y-(CR_4R_4')_p-V-(CH_2)_q-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(5) $-Y-(CR_4R_4')_o-(W)_q-(CR_4R_4')_o-(CH_2)-ONO_2$;

(6) $-Y-(CR_4R_4')_p-(W)_q-(T)_o-(CR_4R_4')_o-(CH_2)-ONO_2$;

(7) $-Y-(CR_4R_4')_q-C(Z)-V-(CR_4R_4')_q-(CH_2)-ONO_2$;

(8) $-Y-(CR_4R_4')_p-V-(CR_4R_4')_p-(CH_2)-ONO_2$;

(9) $-Y-(CR_4R_4')_p-V-(CH_2)_q-(T)_o-(CR_4R_4')_q-(CH_2)-ONO_2$;

R_4 and R_4' at each occurrence are independently a hydrogen, lower alkyl group, -OH, $-CH_2OH$, $-ONO_2$, $-NO_2$ or $-CH_2ONO_2$; or R_4 and R_4' taken together with the carbon atom to which they are attached are a cycloalkyl group or a heterocyclic ring;

V is -C(O)-T-, -T-C(O)-, -T-C(O)-T or T-C(O)-C(O)-T;

W is a covalent bond or a carbonyl group;

T at each occurrence is independently an oxygen, $(S(O)_o)_o$ or NR_j;

R_j is a hydrogen, an alkyl group, an aryl group, a heterocyclic ring, an alkylcarbonyl group, an alkylaryl group, an alkylsulfinyl group, an alkylsulfonyl group, an arylsulfinyl group, an arylsulfonyl group, a sulfonamido group, a N-alkylsulfonamido group, a N,N-diarylsulfonamido group, a N-arylsulfonamido group, a N-alkyl-N-arylsulfonamido group, a carboxamido group or a hydroxyl group;

p at each occurrence is independently an integer from 1 to 6;

q at each occurrence is independently an integer from 1 to 3;

o at each occurrence is independently an integer from 0 to 2;

Y is oxygen or sulfur (-S-);

B is either phenyl or $(CH_2)_o$;

Q' is a cycloalkyl group, a heterocyclic ring or an aryl group;

Z is (=O), $(=N-OR_5)$, $(=N-NR_5R'_5)$ or $(=CR_5R'_5)$;

M and M' are each independently $-O^- H_3N^+-(CR_4R'_4)_q-CH_2ONO_2$ or $-T-(CR_4R'_4)_o-CH_2ONO_2$;

R_5 and R_5' at each occurrence are independently a hydrogen, a hydroxyl group, an alkyl group, an aryl group, an alkylsulfonyl group, an arylsulfonyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group, an alkoxyaryl group, a cycloalkyl group or a heterocyclic ring; and

with the proviso that for X in the compounds of Formulas (I)

when Y is oxygen or sulfur in Formula 5, and W is a covalent bond, at least one R_4 or R_4' must be –OH, $-ONO_2$, $-NO_2$ or $-CH_2ONO_2$ or R_4 and R_4' taken together with the carbon atom to which they are attached are a cycloalkyl group or a heterocyclic ring;

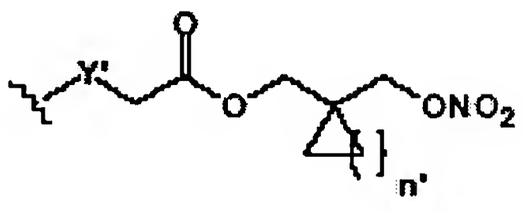
when Y is oxygen or sulfur in Formula 6, T is $-N(CH_3)$, W is a covalent bond and R_4 and R_4' are hydrogen, p cannot be the integer 2, and o cannot be the integer 1 in $-(CR_4R'_4)_o$;

when Y is oxygen or sulfur in Formula 6, W is a covalent bond, T is oxygen and o is the integer 1, at least one R_4 or R_4' must be –OH, $-NO_2$ or $-CH_2ONO_2$ or R_4 and R_4' taken together with the carbon atom to which they are attached are a cycloalkyl group or a heterocyclic ring.

2. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

3. The compound of claim 1, wherein X is:

(1)



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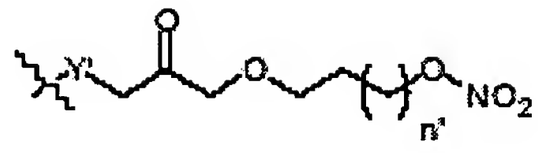

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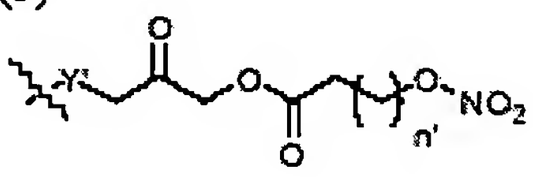

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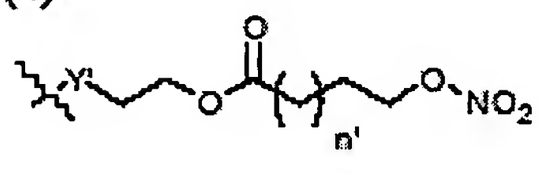

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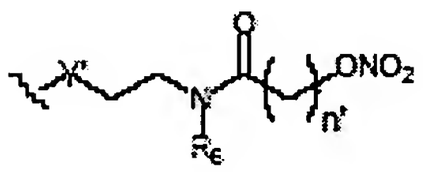

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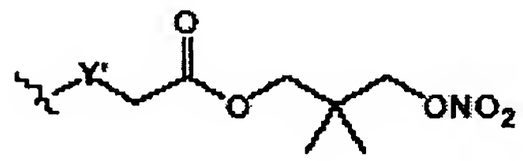

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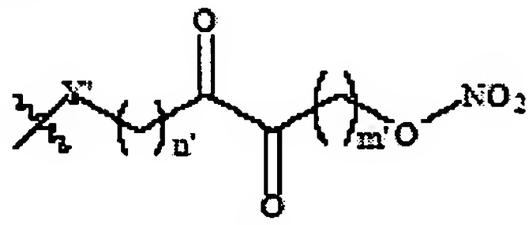
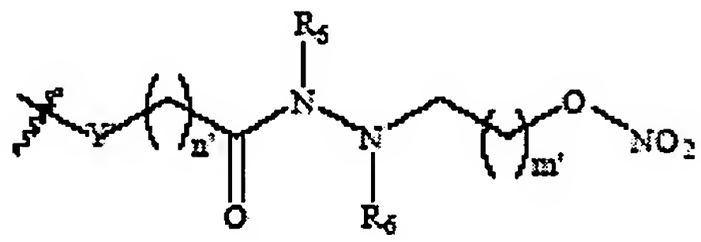


(8)

(9)



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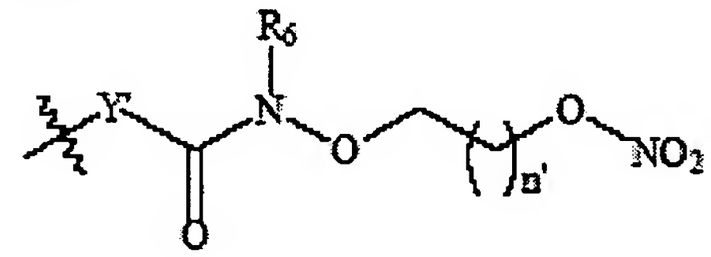

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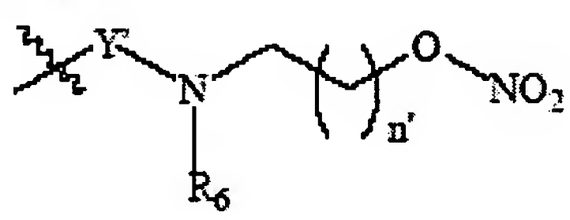

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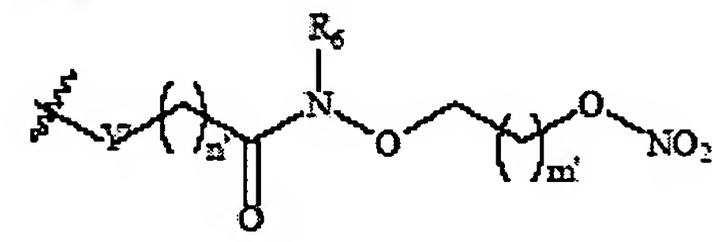
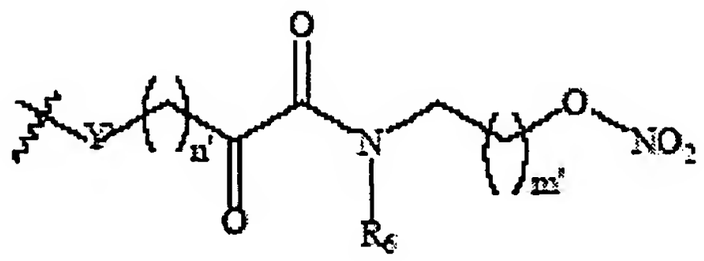
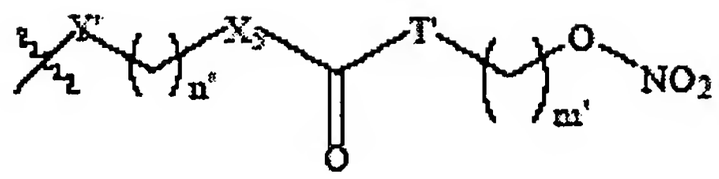


(13)

(14)





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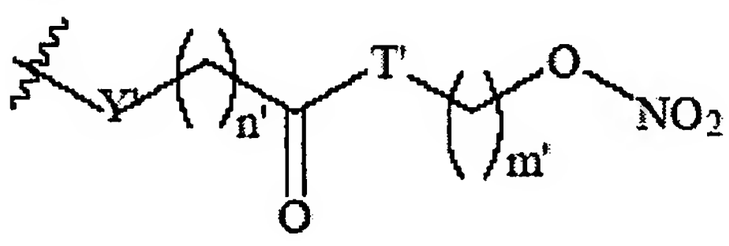

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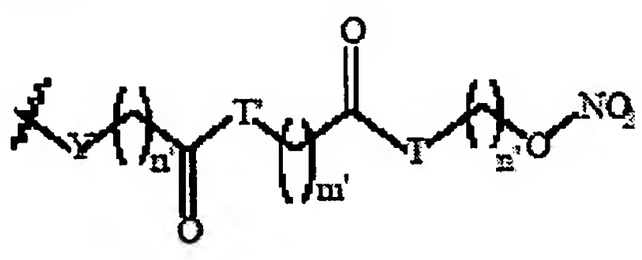

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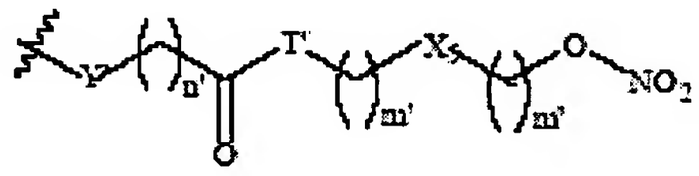

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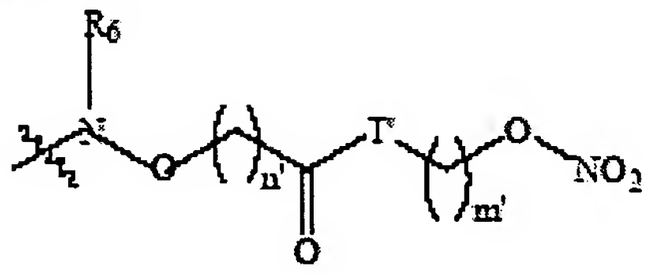

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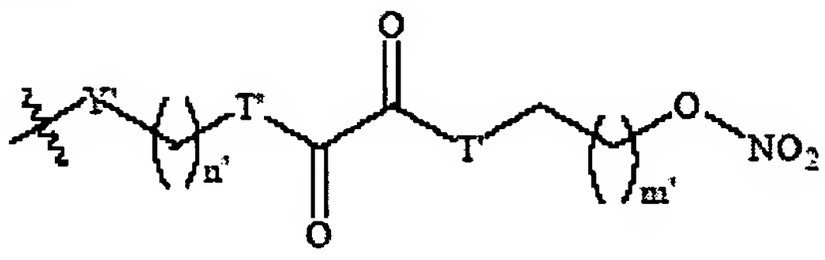

wherein:

Y' is oxygen or sulfur;

T' is oxygen, sulfur or NR_6;

X_5 is oxygen, $(S(O)_o)_o$ or NR_6;

R_6 is a hydrogen, a lower alkyl group, an aryl group;

R_7 is a lower alkyl group or an aryl group;

R_8 at each occurrence is independently is a hydrogen, a hydroxyl group, a lower alkyl group, an aryl group, $-NO_2$, $-CH_2-ONO_2$ or $-CH_2-OH$;

n' and m' are each independently an integer from 0 to 10;

o is as defined herein.

4. The compound of claim 1, wherein the compound of Formula (I) is a nitrosated acemetacin, a nitrosated aceclofenac, a nitrosated alminoprofen, a nitrosated amfenac, a nitrosated bendazac, a nitrosated benoxaprofen, a nitrosated bromfenac, a nitrosated bucloxic acid, a nitrosated butibufen, a nitrosated carprofen, a nitrosated cinmetacin, a nitrosated clopirac, a nitrosated diclofenac, a nitrosated etodolac, a nitrosated felbinac, a nitrosated fenclozic acid, a nitrosated fenbufen, a nitrosated fenoprofen, a nitrosated fentiazac, a nitrosated flunoxaprofen, a nitrosated flurbiprofen, a nitrosated ibufenac, a nitrosated ibuprofen, a nitrosated indomethacin, a nitrosated isofezolac, a nitrosated isoxepac, a nitrosated indoprofen, a nitrosated ketoprofen, a nitrosated lonazolac, a nitrosated loxoprofen, a nitrosated metiazinic acid, a nitrosated mofezolac, a nitrosated miroprofen, a nitrosated naproxen, a nitrosated oxaprozin, a nitrosated pirozolac, a nitrosated pirprofen, a nitrosated pranoprofen, a nitrosated protizinic acid, a nitrosated salicylamide, a nitrosated sulindac, a nitrosated suprofen, a nitrosated suxibuzone, a nitrosated tiaprofenic acid, a nitrosated tolmetin, a nitrosated xenbucin, a nitrosated ximoprofen, a nitrosated zaltoprofen a nitrosated zomepirac; the compound of Formula II is a nitrosated aspirin, a nitrosated acemetcin, a nitrosated bumadizon, a nitrosated carprofenac, a nitrosated clidanac, a nitrosated diflunisal, a nitrosated enfenamic acid, a nitrosated fendosal, a nitrosated flufenamic acid, a nitrosated flunixin, a nitrosated gentisic acid, a nitrosated ketorolac, a nitrosated meclofenamic acid, a nitrosated mefenamic acid, a nitrosated mesalamine, a nitrosated niflumic acid, a nitrosated salsalate, a nitrosated tolfenamic acid or a nitrosated tropensin.

5. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

6. A method for treating a gastrointestinal disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

7. The method of claim 6, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, constipation, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

8. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

9. The method of claim 8, wherein the wound is an ulcer.

10. A method for treating or reversing gastrointestinal, renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

11. A method for treating an inflammatory disease in patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

12. The method of claim 11, wherein the inflammatory disease is a cardiovascular disorder, reperfusion injury to an ischemic organ, angiogenisis, arthritis, asthma, bronchitis, premature labor, tendinitis, bursitis, an autoimmune disease, an immunological disorder, a skin-related condition, neoplasia, an inflammatory process in a disease, pulmonary inflammation, a central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, a microbial infection, a bacterial-induced inflammation, a viral induced inflammation, a urinary disorder, a urological disorder, endothelial dysfunction, organ deterioration, tissue deterioration, a sexual dysfunction or activation, adhesion and infiltration of neutrophils at the site of inflammation.

13. The method of claim 12, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

14. The method of claim 12, wherein the central nervous system disorder is cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, memory loss or central nervous system damage resulting from stroke, ischemia or trauma.

15. A method for treating an ophthalmic disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 2.

16. The composition of claim 2, further comprising at least one therapeutic agent.

17. The composition of claim 16, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a cyclooxygenase inhibitor, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4 receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a 3-hydroxy-3-methylglutaryl coenzyme A inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

18. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 16.

19. A method for treating a gastrointestinal disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 16.

20. The method of claim 19, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, constipation, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

21. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 16.

22. The method of claim 21, wherein the wound is an ulcer.

23. A method for treating or reversing gastrointestinal, renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 16.

24. A method for for treating an inflammatory disease in patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 16.

25. The method of claim 24, wherein the inflammatory disease is a cardiovascular disorder, reperfusion injury to an ischemic organ, angiogenisis, arthritis, asthma, bronchitis, premature labor, tendinitis, bursitis, an autoimmune disease, an immunological disorder, a skin-related condition, neoplasia, an inflammatory process in a disease, pulmonary inflammation, a central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, a microbial infection, a bacterial-induced inflammation, a viral induced inflammation, a urinary disorder, a urological disorder, endothelial dysfunction, organ deterioration, tissue deterioration, a sexual dysfunction or activation, adhesion and infiltration of neutrophils at the site of inflammation.

26. The method of claim 25, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

27. The method of claim 25, wherein the central nervous system disorder is cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, memory loss or central nervous system damage resulting from stroke, ischemia or trauma.

28. A method for treating an ophthalmic disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 16.

29. A composition comprising at least one compound of claim 1 and at least one compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase.

30. The composition of claim 29, further comprising a pharmaceutically acceptable carrier.

31. The composition of claim 29, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase is an S-nitrosothiol.

32. The composition of claim 31, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, or S-nitroso-cysteinyl-glycine.

33. The composition of claim 31, wherein the S-nitrosothiol is:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring. a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, an arylsulfonyloxy, a urea, a nitro, -T-Q-, or $-(C(R_g)(R_h))_k$-T-Q or R_e and R_f taken together are an oxo, a thial, a heterocyclic ring, a cycloalkyl group, an oxime, a hydrazone or a bridged cycloalkyl group; Q is -NO or $-NO_2$; and T is independently a covalent bond, a carbonyl, an oxygen, $-S(O)_o-$ or $-N(R_a)R_i-$, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyloxy, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, $-CH_2\text{-}C(T\text{-}Q)(R_g)(R_h)$, or $-(N_2O_2-)^-\bullet M^+$, wherein M^+ is an organic or inorganic cation; with the

proviso that when R_i is $-CH_2-C(T-Q)(R_g)(R_h)$ or $-(N_2O_2-)\bullet M^+$; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group; and R_g and R_h at each occurrence are independently R_e.

34. The composition of claim 29, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated L-homoarginine, nitrosylated L-homoarginine), citrulline, ornithine, glutamine, lysine, an arginase inhibitor or a nitric oxide mediator.

35. The composition of claim 29, wherein the compound that donates, transfers, or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase is:

(i) a compound that comprises at least one ON-O- or ON-N- group;

(ii) a compound that comprises at least one O_2N-O-, O_2N-N- or O_2N-S- or group;

(iii) a N-oxo-N-nitrosoamine having the formula: $R^{1''}R^{2''}N-N(O-M^+)-NO$, wherein $R^{1''}$ and $R^{2''}$ are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M^+ is an organic or inorganic cation.

36. The composition of claim 35, wherein the compound comprising at least one ON-O- or ON-N- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, an ON-O-heterocyclic compound or an ON-N-heterocyclic compound.

37. The composition of claim 35, wherein compound comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group is an O_2N-O-polypeptide, an O_2N-N-polypeptide, an O_2N-S-polypeptide, an O_2N-O-amino acid, O_2N-N-amino acid, O_2N-S-amino acid, an O_2N-O-sugar, an O_2N-N-sugar, O_2N-S-sugar, an O_2N-O-oligonucleotide, an O_2N-N-oligonucleotide, an O_2N-S-

oligonucleotide, , a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-O-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O_2N-S-hydrocarbon, an O_2N-O-heterocyclic compound, an O_2N-N-heterocyclic compound or an O_2N-S-heterocyclic compound.

38. The composition of claim 29, further comprising at least one therapeutic agent.

39. The composition of claim 38, wherein the therapeutic agent is a steroid, a nonsteroidal antiinflammatory compound, a cyclooxygenase-2 inhibitor, a 5-lipoxygenase (5-LO) inhibitor, a leukotriene B_4 receptor antagonist, a leukotriene A_4 hydrolase inhibitor, a 5-HT agonist, a HMG CoA inhibitor, a H_2 antagonist, an antineoplastic agent, an antiplatelet agent, a thrombin inhibitor, a thromboxane inhibitor, a decongestant, a diuretic, a sedating or non-sedating anti-histamine, an inducible nitric oxide synthase inhibitor, an opioid, an analgesic, a *Helicobacter pylori* inhibitor, a proton pump inhibitor, an isoprostane inhibitor, or a mixture of two or more thereof.

40. A method for treating or reducing inflammation, pain or fever in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 38.

41. A method for treating a gastrointestinal disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 38.

42. The method of claim 41, wherein the gastrointestinal disorder is an inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, constipation, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding ulcer, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a bacterial infection, short-bowel (anastomosis) syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

43. A method for facilitating wound healing in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 38.

44. The method of claim 43, wherein the wound is an ulcer.

45. A method for treating or reversing gastrointestinal, renal and/or respiratory toxicity in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 38.

46. A method for treating inflammatory disease in patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 38.

47. The method of claim 46, wherein the inflammatory disease is a cardiovascular disorder, reperfusion injury to an ischemic organ, angiogenisis, arthritis, asthma, bronchitis, premature labor, tendinitis, bursitis, an autoimmune disease, an immunological disorder, a skin-related condition, neoplasia, an inflammatory process in a disease, pulmonary inflammation, a central nervous system disorder, allergic rhinitis, respiratory distress syndrome, endotoxin shock syndrome, a microbial infection, a bacterial-induced inflammation, a viral induced inflammation, a urinary disorder, a urological disorder, endothelial dysfunction, organ deterioration, tissue deterioration, a sexual dysfunction or activation, adhesion and infiltration of neutrophils at the site of inflammation.

48. The method of claim 47, wherein the neoplasia is a brain cancer, a bone cancer, an epithelial cell-derived neoplasia (epithelial carcinoma), a basal cell carcinoma, an adenocarcinoma, a gastrointestinal cancer, a lip cancer, a mouth cancer, an esophageal cancer, a small bowel cancer, a stomach cancer, a colon cancer, a liver cancer, a bladder cancer, a pancreas cancer, an ovary cancer, a cervical cancer, a lung cancer, a breast cancer, a skin cancer, a squamus cell cancer, a basal cell cancer, a prostate cancer, a renal cell carcinoma, a cancerous tumor, a growth, a polyp, an adenomatous polyp, a familial adenomatous polyposis or a fibrosis resulting from radiation therapy.

49. The method of claim 47, wherein the central nervous system disorder is cortical dementia, Alzheimer's disease, vascular dementia, multi-infarct dementia, pre-senile dementia, alcoholic dementia, senile dementia, memory loss or central nervous system damage resulting from stroke, ischemia or trauma.

50. A method for treating an ophthalmic disorder in a patient in need thereof comprising administering to the patient a therapeutically effective amount of the composition of claim 29 or 38.

51. A kit comprising at least one compound of claim 1.

52. The kit of claim 51, further comprising (i) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; (ii) at least one therapeutic agent; or (iii) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent.

53. The kit of claim 52, wherein the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; the at least one therapeutic agent; or the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent; are in the form of separate components in the kit

54. A kit comprising the composition of claim 16, 29 or 38.

55. A compound selected from the group consisting of

2-(N-(2-(nitrooxy)ethyl)carbamoyloxy)ethyl (2S)-2-(6-methoxy(2-naphthyl))propanoate;

(N-methyl-N-(2-(nitrooxy)ethyl)carbamoyl)methyl (2S)-2-(6-methoxy(2-naphthyl))propanoate;

(N-ethyl-N-(2-(nitrooxy)ethyl)carbamoyl)methyl (2S)-2-(6-methoxy(2-naphthyl))propanoate;

(N-methyl-N-(((2-(nitrooxy)ethyl)oxycarbonyl)methyl)carbamoyl)methyl (2S)-2-(6-methoxy(2-naphthyl))propanoate;

(N-methyl-N-(((3-(nitrooxy)propyl)oxycarbonyl)methyl)carbamoyl)methyl (2S)-2-(6-methoxy(2-naphthyl))propanoate;

(N-methyl-N-((N-(2-(nitrooxy)ethyl)carbamoyl)methyl)carbamoyl)methyl (2S)-2-(6-methoxy(2-naphthyl))propanoate;

((2-(nitrooxy)ethyl)oxycarbonyl)methyl 2-(6-methoxy-2-naphthyl)propanoate;

(N-(3-(nitrooxy)propyl)carbamoyl)methyl 2-(6-methoxy-2-naphthyl)propanoate;

((2-((2-(nitrooxy)ethyl)sulfonyl)ethyl)oxycarbonyl)methyl 2-(6-methoxy-2-naphthyl)propanoate;

(2S)-2-(6-methoxy(2-naphthyl))-N-((N-(2-(nitrooxy)ethyl)carbamoyl) methoxy)propanamide;

(N-methyl-N-(3-(nitrooxy)propyl)carbamoyl)methyl (2S)-2-(6-methoxy(2-naphthyl))propanoate;

2-((2S)-2-(6-methoxy(2-naphthyl))propanoyloxy)ethyl 3-(nitrooxy)-propyl ethane-1,2-dioate;

N-((2S)-2-(6-methoxy(2-naphthyl))propanoylamino)-4 (nitrooxy)butanamide;

or a pharmaceutically acceptable salt thereof.

56. A composition comprising at least one compound of claim 55 and a pharmaceutically acceptable carrier.

57. The composition of claim 56, further comprising (i) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase; (ii) at least one therapeutic agent; or (iii) at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase and at least one therapeutic agent.

58. A kit comprising at least one compound of claim 55.